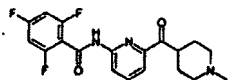


Remarks

Applicants elect the invention of Group I, drawn to compounds and compositions of formula I. Applicants believe that the Examiner has incorrectly applied the Restriction Requirement to claims 1-33 as-filed in the corresponding PCT application no. PCT/US03/08455. Applicants note that the claims were amended upon National Stage Entry and assert that the Restriction Requirement should be applied to these claims as amended on September 28, 2004. Applicants enclose a copy of the Preliminary Amendment filed on September 28, 2004. This election is made without traverse.

The Examiner also required election of a species to be examined. Accordingly, Applicants elect the compound of Example 21 in the as-filed PCT application:



Upon entry of the present amendment, claims 1-7, 9-14, 27-58 are pending. Claims 8 and 15-26 have been canceled. Claims 1-7 and 46-58 read on the elected invention. Claims 9-14 and 27-45 have been withdrawn. Applicants reserve the right to request rejoinder of the withdrawn claims in accordance with the provisions of MPEP § 821.04.

Claims 6 and 7 have been amended. Support for the amendment is found at page 12, line 4 of the as-filed PCT specification. Accordingly, no new matter has been added.

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
for: [Signature] Reg. # 57,977
 (for R. Elrif, Reg. No. 39,529)
 Attorney for Applicants
 c/o MINTZ, LEVIN
 One Financial Center
 Tel: (617) 542-6000
 Fax: (617) 542-2241
 Customer No. 30623

Dated: July 23, 2007

Doc # 4098403



"Express Mail" mailing label number <u>EL832896926 US</u>	Date of Deposit <u>9-28-04</u>
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.	
<u>Bruce Thomas</u> Printed Name	<u>Bruce Thomas</u> Signature

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Michael Philip Cohen, et al.
For : PYRIDINOYLPIPERIDINES AS 5-HT1F AGONISTS
Docket No. : X-14075

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Arlington, VA 22202
Sir:

Introductory Comments

Please amend the accompanying application as follows:

COPY

Amendments to the Specification

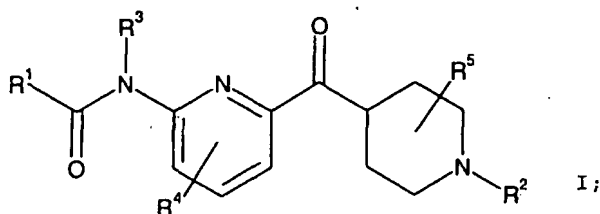
At page 1, Please insert the following new first paragraph, immediately following the title:

This U.S. national stage application of International Application PCT/US 03/08455, filed March 27, 2003, claims priority to U.S. provisional application Serial Number 60/369,088, filed March 29, 2002.

On a new separate last page after the Claims, please insert the following abstract:

ABSTRACT

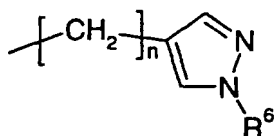
The present invention relates to compounds of formula I:



or pharmaceutically acceptable acid addition salts thereof, where;

R¹ is C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, substituted C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl-C₁-C₃ alkyl, substituted C₃-C₇ cycloalkyl-C₁-C₃ alkyl, phenyl, substituted phenyl, heterocycle, or substituted heterocycle;

R² is hydrogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl-C₁-C₃ alkyl, or a group of formula II



II;

R³ is hydrogen or C₁-C₃ alkyl;

R⁴ is hydrogen, halo, or C₁-C₃ alkyl;

R⁵ is hydrogen or C₁-C₃ alkyl;

R⁶ is hydrogen or C₁-C₆ alkyl; and

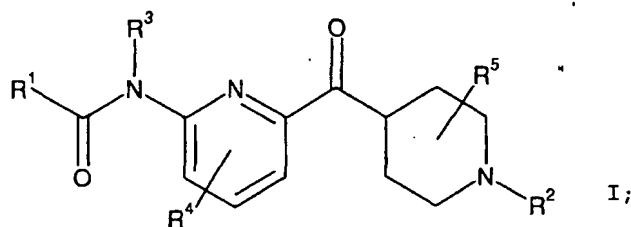
n is an integer from 1 to 6 inclusively.

The compounds of the present invention are useful for activating 5-HT_{1F} receptors, inhibiting neuronal protein extravasation, and for the treatment or prevention of migraine in a mammal. The present invention also relates to a process for the synthesis of intermediates in the synthesis of compounds of Formula I.

Amendments to the Claims

Please amend the claims as follows:

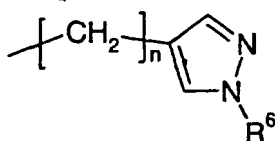
1. (Original) A compound of formula I:



or a pharmaceutically acceptable acid addition salt thereof, where;

R¹ is C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, substituted C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl-C₁-C₃ alkyl, substituted C₃-C₇ cycloalkyl-C₁-C₃ alkyl, phenyl, substituted phenyl, heterocycle, or substituted heterocycle;

R² is hydrogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl-C₁-C₃ alkyl, or a group of formula II



II;

R³ is hydrogen or C₁-C₃ alkyl;

R⁴ is hydrogen, halo, or C₁-C₃ alkyl;

R⁵ is hydrogen or C₁-C₃ alkyl;

R⁶ is hydrogen or C₁-C₆ alkyl; and

n is an integer from 1 to 6 inclusively.

2. (Original) The compound Claim 1 wherein R⁵ is hydrogen and R⁴ is hydrogen or halogen.

3. (Original) The compound of Claim 2 wherein R⁴ is hydrogen.

4. (Original) The compound of any one of Claims 1 – 3 wherein R² is hydrogen or C₁ – C₃ alkyl.

5. (Currently amended) The compound of ~~any one of Claims 1 – 4~~ Claim 1 wherein R¹ is phenyl, substituted phenyl, heterocycle, or substituted heterocycle.

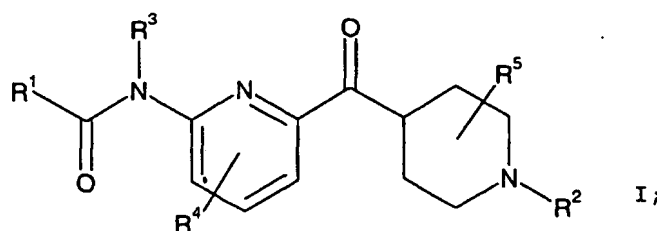
6. (Currently amended) The compound of ~~any one of Claims 1 – 5~~ Claim 1 wherein R¹ is phenyl, substituted phenyl, heterocycle or substituted heterocycle, wherein the heterocycle moiety is selected from the group consisting of furanyl, thiophenyl, pyrrolyl, pyrrolidinyl, pyridinyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, thiazolidinyl, N-acetylthiazolidinyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoquinolinyl, benzoxazolyl, benzodioxolyl, benzothiazolyl, quinolinyl, benzofuranyl, benzothiophenyl, and indolyl, and wherein ~~substituted is taken to mean the ring moiety is substituted with one to three halo substituents; or substituted with one to two substituents independently selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ alkylthio, wherein each alkyl, alkoxy and alkylthio substituent can be further substituted independently with C₁-C₂ alkoxy or with one to five halo groups each independently selected from fluoro and chloro; or substituted with one substituent selected from the group consisting of phenyloxy, benzyloxy, phenylthio, benzylthio, and pyrimidinyl, wherein the phenyloxy, benzyloxy, phenylthio, benzylthio, or pyrimidinyl moiety can be further substituted with one to two substituents selected from the group consisting of halo, C₁-C₂ alkyl, and C₁-C₂ alkoxy; or substituted with one substituent selected from the group consisting of C₁-C₄ acyl and C₁-C₄ alkoxycarbonyl, and further substituted with zero to one substituent selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ alkylthio.~~

7. (Currently amended) The compound of Claim ~~6~~ 1 wherein R¹ is phenyl, substituted phenyl, heterocycle or substituted heterocycle, wherein the heterocycle moiety is selected from the group consisting of pyridinyl, indolyl, benzofuranyl, furanyl, thiophenyl, benzodioxolyl, and thiazolidinyl, and wherein substituted is taken to mean the ring moiety is substituted with one to three halo substituents; or substituted with one to two substituents independently selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ alkylthio, wherein each alkyl, alkoxy and alkylthio substituent can be further substituted independently with C₁-C₂ alkoxy or with one to five halo groups each independently selected

from fluoro and chloro; or substituted with one substituent selected from the group consisting of phenyloxy, benzyloxy, phenylthio, benzylthio, and pyrimidinyl, wherein the phenyloxy, benzyloxy, phenylthio, benzylthio, or pyrimidinyl moiety can be further substituted with one to two substituents selected from the group consisting of halo, C₁-C₂ alkyl, and C₁-C₂ alkoxy; or substituted with one substituent selected from the group consisting of C₁-C₄ acyl and C₁-C₄ alkoxy, and further substituted with zero to one substituent selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ alkylthio.

8. (Cancelled)

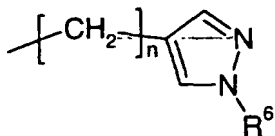
9. (Original) A method for activating 5-HT_{1F} receptors in a mammal comprising administering to a mammal in need of such activation an effective amount of a compound of formula I:



or a pharmaceutically acceptable acid addition salt thereof, where;

R¹ is C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, substituted C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl-C₁-C₃ alkyl, substituted C₃-C₇ cycloalkyl-C₁-C₃ alkyl, phenyl, substituted phenyl, heterocycle, or substituted heterocycle;

R² is hydrogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl-C₁-C₃ alkyl, or a group of formula II



II;

R³ is hydrogen or C₁-C₃ alkyl;

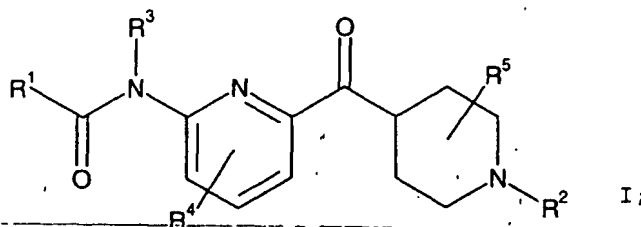
R⁴ is hydrogen, halo, or C₁-C₃ alkyl;

R⁵ is hydrogen or C₁-C₃ alkyl;

R^6 is hydrogen or C_1 - C_6 alkyl; and
 n is an integer from 1 to 6 inclusively.

10. (Original) The method according to Claim 9 wherein the mammal is a human.

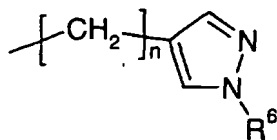
11. (Original) A method for inhibiting neuronal protein extravasation in a mammal comprising administering to a mammal in need of such inhibition an effective amount of a compound of formula I:



or a pharmaceutically acceptable acid addition salt thereof, where;

R^1 is C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, substituted C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyl- C_1 - C_3 alkyl, substituted C_3 - C_7 cycloalkyl- C_1 - C_3 alkyl, phenyl, substituted phenyl, heterocycle, or substituted heterocycle;

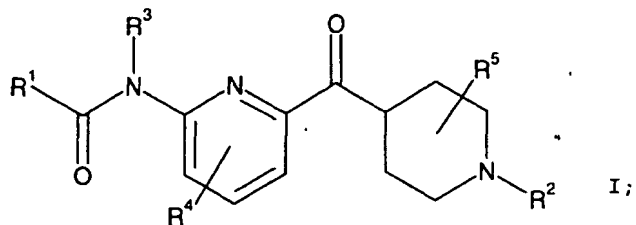
R^2 is hydrogen, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl- C_1 - C_3 alkyl, or a group of formula II



II:

R^3 is hydrogen or C_1 - C_3 alkyl;
 R^4 is hydrogen, halo, or C_1 - C_3 alkyl;
 R^5 is hydrogen or C_1 - C_3 alkyl;
 R^6 is hydrogen or C_1 - C_6 alkyl; and
 n is an integer from 1 to 6 inclusively.

12. (Original) The method according to Claim 11 wherein the mammal is a human.



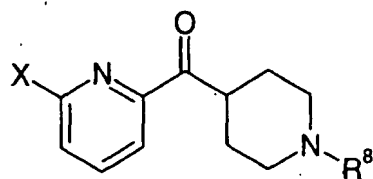
R¹ is C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, substituted C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl-C₁-C₃ alkyl, substituted C₃-C₇ cycloalkyl-C₁-C₃ alkyl, phenyl, -substituted phenyl, heterocycle, or substituted heterocycle;

$$\left[\text{CH}_2 - \text{C} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \right]_n \text{R}^6$$

n is an integer from 1 to 6 inclusively.

15-26. (Cancelled)

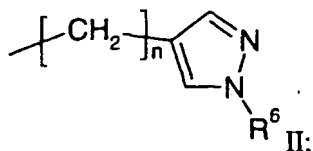
-8-



III

where X is bromo or chloro;

R^8 is an amino protecting group, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl- C_1 - C_3 alkyl, or a group of formula II

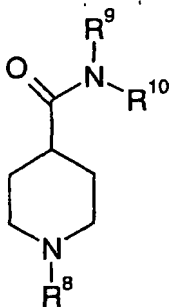


R^6 is hydrogen or C_1 - C_6 alkyl; and

n is an integer from 1 to 6 inclusively;

comprising

- 1) reacting a 2,6-dihalopyridine selected from 2,6-dibromopyridine and 2,6-dichloropyridine, with *n*-butyl lithium to form 2-halo-6-lithium-pyridine, and then
- 2) reacting the 2-halo-6-lithium-pyridine with a substituted aminocarbonylpiperidine compound of formula IV



IV

wherein R^8 and R^{10} are each methyl, or R^9 and R^{10} , together with the nitrogen to which they are attached, combine to form azetidiny, pyrrolidinyl, or piperidinyl.

28. (Original) The process of Claim 27 wherein X is bromo and the 2,6-dihalopyridine is 2,6-dibromopyridine.

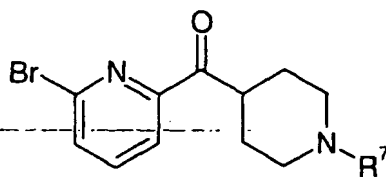
29. (Currently amended) The process of ~~either Claim 27 or Claim 28~~ wherein R^9 and R^{10} are each methyl.

30. (Currently amended) The process of ~~either Claim 27 or Claim 28~~ wherein R^9 and R^{10} , together with the nitrogen to which they are attached, combine to form pyrrolidinyl.

31. (Currently amended) The process of ~~any of Claims 27-30~~ Claim 27 wherein the solvent for step 2) is methyl-*t*-butylether.

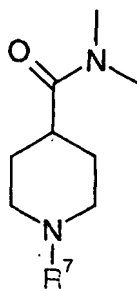
32. (Currently amended) The process of ~~any of Claims 27-30~~ Claim 27 wherein the solvent for step 2) is toluene.

33. (Original) A method for preparing a 2-bromo-6-(piperidin-4-carbonyl)pyridine compound of formula III



III

wherein R^7 is C_1 - C_3 n-alkyl, or an amino protecting group;
comprising reacting 2,6-dibromopyridine with n-butyl lithium to form 2-bromo-6-lithium-pyridine, and then reacting the 2-bromo-6-lithium-pyridine with a 4-(N,N'-dimethylamino)carbonyl piperidine compound of formula IV



IV

in a methyl-*tert*-butyl ether solvent.

34. (New) The process of Claim 28 wherein R^9 and R^{10} are each methyl.

35. (New) The process of Claim 28 wherein R^9 and R^{10} , together with the nitrogen to which they are attached, combine to form pyrrolidinyl.

36. (New) The process of Claim 28 wherein the solvent for step 2) is methyl-*t*-butylether.

37. (New) The process of Claim 29 wherein the solvent for step 2) is methyl-*t*-butylether.

38. (New) The process of Claim 30 wherein the solvent for step 2) is methyl-*t*-butylether.

39. (New) The process of Claim 34 wherein the solvent for step 2) is methyl-*t*-butylether.

40. (New) The process of Claim 35 wherein the solvent for step 2) is methyl-*t*-butylether.

41. (New) The process of Claim 28 wherein the solvent for step 2) is toluene.

42. (New) The process of Claim 29 wherein the solvent for step 2) is toluene.

43. (New) The process of Claim 30 wherein the solvent for step 2) is toluene.

44. (New) The process of Claim 34 wherein the solvent for step 2) is toluene.

45. (New) The process of Claim 35 wherein the solvent for step 2) is toluene.

46. (New) The compound of Claim 5 wherein R^3 is hydrogen and R^4 is hydrogen or halogen.

47. (New) The compound of Claim 46 wherein R^4 is hydrogen.

48. (New) The compound of any one of Claims 5, 46, or 47 wherein R^2 is hydrogen or $C_1 - C_3$ alkyl.

49. (New) The compound of Claim 6 wherein R⁵ is hydrogen and R⁴ is hydrogen or halogen.

50. (New) The compound of Claim 49 wherein R⁴ is hydrogen.

51. (New) The compound of any one of Claims 6, 49, or 50, wherein R² is hydrogen or C₁ – C₃ alkyl.

52. (New) The compound of Claim 7 wherein R⁵ is hydrogen and R⁴ is hydrogen or halogen.

53. (New) The compound of Claim 52 wherein R⁴ is hydrogen.

54. (New) The compound of any one of Claims 7, 52, or 53 wherein R² is hydrogen or C₁ – C₃ alkyl.

55. (New) A pharmaceutical formulation comprising a compound of any one of Claims 1 – 7, 46-54 and a pharmaceutical carrier, diluent, or excipient.

56. (New) The compound 2,4,6-trifluoro-N-[6-[(1-methyl-4-piperidiny)carbonyl]-2-pyridiny]-benzamide or a pharmaceutically acceptable acid addition salt thereof.

57. (New) The compound 2,4,6-trifluoro-N-[6-[(1-methyl-4-piperidiny)carbonyl]-2-pyridiny]-benzamide hemisuccinate salt.

58. (New) The compound 2,4,6-trifluoro-N-[6-[(1-methyl-4-piperidiny)carbonyl]-2-pyridiny]-benzamide hydrochloride salt.

Remarks

The specification has been amended to include a claim to priority in compliance with 35 U.S.C. §119(e), and an abstract in compliance with 37 C.F.R. §1.72(b). Claims 5-7 and 29-32 are amended and new Claims 34-54 are added to remove the multiple dependency of claims dependent from multiply dependent claims. Claim 8 is cancelled without prejudice in favor of new Claim 55, which takes into account new Claims 34-54. Claims 15-26 have been cancelled without prejudice in that they are drawn to pharmaceutical uses in claim formats not favored under U.S. patent law, and in that their subject matter is otherwise effectively protected by the corresponding method of treatment claims, Claims 9-14. New Claims 56-58 are directed to particular preferred embodiments of the invention as set further in the Specification, particularly at examples 8, 22, and 23. No new subject matter is added.

Respectfully submitted,



R. Craig Tucker
Attorney for Applicants
Registration No. 45,165
Phone: 317-433-9829

Eli Lilly and Company
Patent Division / RCT
P.O. Box 6288
Indianapolis, Indiana 46206-6288

Sept 2, 2004